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NEWS 15	FEB 11	WTEXTILES reloaded and enhanced
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NEWS 20	FEB 23	TOXCENTER updates mirror those of MEDLINE - more precise author group fields and 2009 MeSH terms
NEWS 21	FEB 23	Three million new patent records blast AEROSPACE into STN patent clusters
NEWS 22	FEB 25	USGENE enhanced with patent family and legal status display data from INPADOCDB
NEWS 23	MAR 06	INPADOCDB and INPAFAMDB enhanced with new display formats

NEWS EXPRESS JUNE 27 08 CURRENT WINDOWS VERSION IS V8.3,

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=> FIL HCAPLUS

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FULL ESTIMATED COST	0.22	0.22

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FILE COVERS 1907 - 9 Mar 2009 VOL 150 ISS 11
FILE LAST UPDATED: 8 Mar 2009 (20090308/ED)

HCAplus now includes complete International Patent Classification (IPC) reclassification data for the third quarter of 2008.

CAS Information Use Policies apply and are available at:

http://www.cas.org/legal/infopolicy.html

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s 1h-tetrazol-5-yl biphenyl
265667 1H
4026 TETRAZOL
5 TETRAZOLS

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       6945620 5
        149234 YL
            72 YLS
        149286 YL
                 (YL OR YLS)
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         19368 BIPHENYLS
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        162605 HALIDE
        134568 HALIDES
        233992 HALIDE
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        237618 ARYL
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                 (ARYL(W)MAAGNESIUM)
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=> s l1 and transition metal catalyst
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       1203452 TRANSITION
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        951296 METALS
       2311183 METAL
                 (METAL OR METALS)
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        829879 CATALYSTS
       1068162 CATALYST
                 (CATALYST OR CATALYSTS)
          5907 TRANSITION METAL CATALYST
                 (TRANSITION(W)METAL(W)CATALYST)
L4           0 L1 AND TRANSITION METAL CATALYST

=> s l1 and metal catalyst
       1907898 METAL
        951296 METALS
       2311183 METAL
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                (METAL OR METALS)
        833374 CATALYST
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L5           0 L1 AND METAL CATALYST

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L6           5 L1 AND CATALYST

=> s l6 and process
       2766153 PROCESS
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       4131723 PROCESS
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L7           2 L6 AND PROCESS

=> d l6 ibib abs hitstr tot

L6   ANSWER 1 OF 5  HCAPLUS  COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER:         2008:1186704  HCAPLUS
DOCUMENT NUMBER:          150:5663
TITLE:                    Synthesis and characterization of
                          4'-bromomethyl-2-(N-trityl-1H-
                          tetrazol-5-yl)
                          biphenyl
AUTHOR(S):                Wang, Guo-xi; Sun, Bao-ping; Ru, Zong-ling
CORPORATE SOURCE:         Department of Chemical Engineering, Anyang Institute
                          of Technology, Anyang, 455000, Peop. Rep. China
SOURCE:                   Synthetic Communications (2008), 38(20), 3577-3581
                          CODEN: SYNCAV; ISSN: 0039-7911
PUBLISHER:                Taylor & Francis, Inc.
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB   Biphenyl tetrazole ring is an important component of the Sartan family of
     novel drugs.  4'-Bromomethyl-2-(N-trityl-1H-tetrazol-
     5-yl)biphenyl was synthesized in this article
     from 4'-methyl-2-cyano-biphenyl through three steps.
     4'-Methyl-2-cyano-biphenyl was reacted with azide ions with the help of
     ammonium chloride as catalyst in an autoclave with high
     conversion to afford the tetrazole compds. in 70.6% yield.  After being
     protected by the trityl group with 92.6% yield, 4'-methyl-2-(N-trityl-
     1H-tetrazol-5-yl)biphenyl
     was brominated with N-bromosuccinimide in cyclohexane with
     2,2'-azo-isobutyronitrile acting as an initiator to provide the title
     compound in 83.8% yield.
REFERENCE COUNT:          8      THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS
                                 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6   ANSWER 2 OF 5  HCAPLUS  COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER:         2007:171944  HCAPLUS
```

DOCUMENT NUMBER: 146:229349
TITLE: Process for preparing irbesartan and related angiotensin II receptor antagonists
INVENTOR(S): Bessa Belmunt, Jordi
PATENT ASSIGNEE(S): Farmaprojects, S. A., Spain
SOURCE: PCT Int. Appl., 31pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007017469	A2	20070215	WO 2006-EP65056	20060803
WO 2007017469	A3	20070802		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA				
EP 1749828	A1	20070207	EP 2005-381040	20050804
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, MK, YU				
CA 2617289	A1	20070215	CA 2006-2617289	20060803
EP 1919469	A2	20080514	EP 2006-792689	20060803
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR				
IN 2008KN00447	A	20081017	IN 2008-KN447	20080131
US 20080281097	A1	20081113	US 2008-997715	20080201
CN 101268065	A	20080917	CN 2006-80034419	20080319

PRIORITY APPLN. INFO.:

EP 2005-381040	A	20050804
US 2005-705827P	P	20050804
WO 2006-EP65056	W	20060803

OTHER SOURCE(S): CASREACT 146:229349; MARPAT 146:229349
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention relates to a process for preparing angiotensin II receptor antagonists, in particular irbesartan (I; R = H), and protected forms for the preparation thereof. The process renders irbesartan in one step from intermediates that are easy to obtain from com. products. The reaction is selective for the primary amine and presents no interaction with the NH of the tetrazole ring, which eliminates the need for a protecting group. By the process, irbesartan may be obtained without the need of handling

explosive and highly toxic reagents, such as azide derivs. The process allows for the efficient and simple preparation of irbesartan and related angiotensin II receptor antagonists of formula I (R = H, tetrazolyl protecting group), as illustrated by the following example. Suzuki coupling of 4-bromobenzylamine hydrochloride with 2-(1H-tetrazol-5-yl)phenylboronic acid (reference for preparation is given) gave tetrazolylbiphenyl II. Heterocyclization of valeroyl chloride with 1-aminocyclopentanecarboxylic acid gave oxaazaspirononenone III. Condensation of II with III in the presence of an acid catalyst, such as hydrochloric acid, in a polar aprotic solvent, such as Et acetate, resulted in the formation of irbesartan.

L6 ANSWER 3 OF 5 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2006:623226 HCAPLUS
DOCUMENT NUMBER: 145:271701
TITLE: Regioselective alkylation of 2-alkyl-5,6,7,8-tetrahydro-3H-cycloheptimidazol-4-ones and 2-alkyl-3H-cycloheptimidazol-4-ones
AUTHOR(S): Sonegawa, Motoharu; Yokota, Masayuki; Tomiyama, Hiroshi; Tomiyama, Tsuyoshi
CORPORATE SOURCE: Kotobuki Research Laboratories, Kotobuki Seiyaku Company, Ltd., 6351 Sakaki-Machi, Nagano, 389-0697, Japan
SOURCE: Chemical & Pharmaceutical Bulletin (2006), 54(5), 706-710
CODEN: CPBTAL; ISSN: 0009-2363
PUBLISHER: Pharmaceutical Society of Japan
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 145:271701
AB Regioselective alkylation of 2-alkyl-5,6,7,8-tetrahydro-3H-cycloheptimidazol-4-one and 2-alkyl-3H-cycloheptimidazol-4-one was investigated. 3-[2'-(1-Tert-Butyl-1H-tetrazol-5-yl)biphenyl -4-ylmethyl]-2-propyl-5,6,7,8-tetrahydro-1H-cycloheptimidazol-4-one was preferentially obtained using NaH in DMF or THF. On the other hand, 3-[2'-(1-tert-butyl-1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-2-propyl-5,6,7,8-tetrahydro-3H-cycloheptimidazol-4-one, the synthetic intermediate compound of Pratosartan, was obtained selectively in the presence of Bu4NBr in toluene by using aqueous sodium hydroxide as a base. In this reaction, it was found that the concentration of the alkaline solution influences its regioselectivity. This selectivity was observed even for aldehyde and ester derivs.
REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 4 OF 5 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2005:371249 HCAPLUS
DOCUMENT NUMBER: 142:430273
TITLE: Preparation of candesartan cilexetil
INVENTOR(S): Etinger, Marina Yu; Fedotev, Boris
PATENT ASSIGNEE(S): Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals USA, Inc.; Dolitzky, Ben-Zion
SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005037821	A2	20050428	WO 2004-US34540	20041018
WO 2005037821	A3	20050602		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2542499	A1	20050428	CA 2004-2542499	20041018
US 20050131037	A1	20050616	US 2004-968710	20041018
US 7098342	B2	20060829		
EP 1685126	A2	20060802	EP 2004-795674	20041018
EP 1685126	B1	20070321		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK				
CN 1902192	A	20070124	CN 2004-80037005	20041018
AT 357442	T	20070415	AT 2004-795674	20041018
ES 2284068	T3	20071101	ES 2004-795674	20041018
JP 2005206603	A	20050804	JP 2005-14134	20050121
IN 2006DN01977	A	20070713	IN 2006-DN1977	20060412
US 20060252939	A1	20061109	US 2006-485714	20060712
PRIORITY APPLN. INFO.:			US 2003-512566P	P 20031016
			US 2003-523524P	P 20031118
			US 2004-537995P	P 20040121
			US 2004-568649P	P 20040505
			US 2004-968710	A 20041018
			WO 2004-US34540	W 20041018

OTHER SOURCE(S): CASREACT 142:430273

AB The invention encompasses processes for the synthesis of cilexetil trityl candesartan (I), namely 1-[[(cyclohexyloxy)carbonyl]oxy]ethyl 2-ethoxy-1-[[2'-(1-trityl-1H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylate, from the reaction of trityl candesartan (II), namely 2-ethoxy-1-[[2'-(1-trityl-1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylic acid, with cilexetil halide, i.e. 1-[[(cyclohexyloxy)carbonyl]oxy]ethyl halide, in the presence of a base and a low boiling organic solvent. Optionally, the reaction may be conducted in the presence of a phase transfer catalyst. Thus, a suspension of II (2.0 g), cilexetil chloride (1.21 g), K2CO3 (0.81 g) and MeCN (19 g) was stirred at 40° for .apprx.8 h while monitoring the reaction by TLC. The acetonitrile was removed at 30-35° under reduced pressure (10 mbar) to give, after workup, crude I, as a semisolid of 94.38% pure by HPLC. A solution of I (350 g), toluene (1,050 mL), methanol (2,100 mL) and water (17.0 mL) was refluxed for about 2-4 h, and the solvents were evaporated at 40-50°/100 mbar to give a residue as a viscous oil. The residue was dissolved at 45-55° in a mixture of

toluene/MeOH (1,041 g, 95:5, weight/weight) to give a clear solution which was cooled to -5 to 20°and kept at this temperature for about 8-12 h. The precipitated solids were filtered off, washed on the filter with cold toluene (350 mL) to give candesartan cilexetil as a wet solid (295.8 g, 83.0%). The wet solid (110 g) was dried at 50°/10 mbar for 2-6 h to give a wet white solid (94 g) which was dissolved in absolute ethanol(215-363 mL), filtered, and cooled at -15° to 5° for .apprx.2-24 h. The precipitated solids were filtered off, washed with cold absolute ethanol (23-35 mL),
and dried at 50°/10 mbar to give 21.5 g candesartan cilexetil.

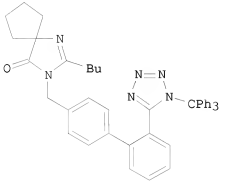
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 5 OF 5 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2004:696369 HCAPLUS
DOCUMENT NUMBER: 141:225515
TITLE: Synthesis of 2-butyl-3-[[2'-(1-trityl-1H-tetrazol-5-yl) biphenyl -4-yl]methyl]-1,3-diazaspiro[4,4]-non-ene-4-one
INVENTOR(S): Nisnevich, Gennady; Rukhman, Igor; Pertsikov, Boris; Kaftanov, Julia; Dolitzky, Ben-zion
PATENT ASSIGNEE(S): Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals Usa, Inc.
SOURCE: PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004072064	A1	20040826	WO 2004-US3604	20040205
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2515138	A1	20040826	CA 2004-2515138	20040205
CA 2640585	A1	20040826	CA 2004-2640585	20040205
US 20040242894	A1	20041202	US 2004-773414	20040205
US 7038060	B2	20060502		
EP 1590343	A1	20051102	EP 2004-708665	20040205
EP 1590343	B1	20080716		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
CN 1771246	A	20060510	CN 2004-80009456	20040205
CN 101239930	A	20080813	CN 2007-10307393	20040205
CN 101239974	A	20080813	CN 2007-10307394	20040205
CN 101239975	A	20080813	CN 2007-10307395	20040205
AT 401323	T	20080815	AT 2004-708665	20040205
ES 2310281	T3	20090101	ES 2004-708665	20040205
IN 2005DN03485	A	20070420	IN 2005-DN3485	20050805

US 20060128967	A1	20060615	US 2006-328966	20060109
US 7312340	B2	20071225		
PRIORITY APPLN. INFO.:			US 2003-445218P	P 20030205
			US 2003-465905P	P 20030428
			CA 2004-2515138	A3 20040205
			CN 2004-80009456	A3 20040205
			US 2004-773414	A3 20040205
			WO 2004-US3604	W 20040205

OTHER SOURCE(S): CASREACT 141:225515
GI



I

AB Provided are 5 methods of making 2-butyl-3-[[2'-(1-trityl-1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1,3-diazaspiro[4,4]non-1-ene-4-one (I), e.g. comprising the steps of: (a) reacting 1-(N'-pentanoylamino)cyclopentanecarboxylic acid amide with 5-(4'-bromomethylbiphenyl-2-yl)-1-trityl-1H-tetrazole in the presence of an inorg. base, a solvent and a phase transfer catalyst; (b) cooling the mixture; (c) adding water to the mixture whereby two phases are obtained; (d) separating the two phases obtained; and (e) recovering the compound I. The compds. I can be converted to irbesartan which is a known angiotensin II receptor antagonist (blocker).

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d l7 ibib abs hitstr tot

L7 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER:	2007:171944 HCAPLUS
DOCUMENT NUMBER:	146:229349
TITLE:	Process for preparing irbesartan and related angiotensin II receptor antagonists
INVENTOR(S):	Bessa Belmunt, Jordi
PATENT ASSIGNEE(S):	Farmaprojects, S. A., Spain
SOURCE:	PCT Int. Appl., 31pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English

FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007017469	A2	20070215	WO 2006-EP65056	20060803
WO 2007017469	A3	20070802		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA				
EP 1749828	A1	20070207	EP 2005-381040	20050804
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, MK, YU				
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R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR				
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PRIORITY APPLN. INFO.:			EP 2005-381040 A	20050804
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			WO 2006-EP65056 W	20060803

OTHER SOURCE(S): CASREACT 146:229349; MARPAT 146:229349
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* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention relates to a process for preparing angiotensin II receptor antagonists, in particular irbesartan (I; R = H), and protected forms for the preparation thereof. The process renders irbesartan in one step from intermediates that are easy to obtain from com. products. The reaction is selective for the primary amine and presents no interaction with the NH of the tetrazole ring, which eliminates the need for a protecting group. By the process, irbesartan may be obtained without the need of handling explosive and highly toxic reagents, such as azide derivs. The process allows for the efficient and simple preparation of irbesartan and related angiotensin II receptor antagonists of formula I (R = H, tetrazolyl protecting group), as illustrated by the following example. Suzuki coupling of 4-bromobenzylamine hydrochloride with 2-(1H-tetrazol-5-yl)phenylboronic acid (reference for preparation is given) gave tetrazolylbiphenyl II. Heterocyclization of valeroyl chloride with 1-aminocyclopentanecarboxylic acid gave oxaazaspirononenone III. Condensation of II with III in the

presence of an acid catalyst, such as hydrochloric acid, in a polar aprotic solvent, such as Et acetate, resulted in the formation of irbesartan.

L7 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2005:371249 HCAPLUS
DOCUMENT NUMBER: 142:430273
TITLE: Preparation of candesartan cilexetil
INVENTOR(S): Etinger, Marina Yu; Fedotev, Boris
PATENT ASSIGNEE(S): Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals USA, Inc.; Dolitzky, Ben-Zion
SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005037821	A2	20050428	WO 2004-US34540	20041018
WO 2005037821	A3	20050602		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
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OTHER SOURCE(S): CASREACT 142:430273
AB The invention encompasses processes for the synthesis of cilexetil trityl candesartan (I), namely 1-[[(cyclohexyloxy)carbonyl]oxy]ethyl 2-ethoxy-1-[[2'-(1-trityl-1H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]methyl]-1H-

benzimidazole-7-carboxylate, from the reaction of trityl candesartan (II), namely 2-ethoxy-1-[[2'-(1-trityl-1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylic acid, with cilexetil halide, i.e. 1-[[(cyclohexyloxy)carbonyl]oxy]ethyl halide, in the presence of a base and a low boiling organic solvent. Optionally, the reaction may be conducted in the presence of a phase transfer catalyst. Thus, a suspension of II (2.0 g), cilexetil chloride (1.21 g), K2CO3 (0.81 g) and MeCN (19 g) was stirred at 40° for .apprx.8 h while monitoring the reaction by TLC. The acetonitrile was removed at 30-35° under reduced pressure (10 mbar) to give, after workup, crude I, as a semisolid of 94.38% pure by HPLC. A solution of I (350 g), toluene (1,050 mL), methanol (2,100 mL) and water (17.0 mL) was refluxed for about 2-4 h, and the solvents were evaporated at 40-50°/100 mbar to give a residue as a viscous oil. The residue was dissolved at 45-55° in a mixture of toluene/MeOH (1,041 g, 95:5, weight/weight) to give a clear solution which was cooled to -5 to 20°and kept at this temperature for about 8-12 h. The precipitated solids were filtered off, washed on the filter with cold toluene (350 mL) to give candesartan cilexetil as a wet solid (295.8 g, 83.0%). The wet solid (110 g) was dried at 50°/10 mbar for 2-6 h to give a wet white solid (94 g) which was dissolved in absolute ethanol(215-363 mL), filtered, and cooled at -15° to 5° for .apprx.2-24 h. The precipitated solids were filtered off, washed with cold absolute ethanol (23-35 mL), and dried at 50°/10 mbar to give 21.5 g candesartan cilexetil.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	52.35	52.57
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-5.74	-5.74

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